A commentary by Scott A. Rodeo, MD, is linked to the online version of this article at jbjs.org.

International Expert Consensus on a Cell Therapy Communication Tool: DOSES

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Background: The lack of a standardized system for describing cell therapies acts as a barrier to advancement in clinical and basic research and practice. The aim of this study was to establish an international expert consensus on strategies to improve standardization and transparency when describing cell therapies. The secondary aim was to develop a consensus among experts on the contents of a standardized tool for describing cell therapies.

Methods: The need for expert consensus on strategies to improve cell therapy communication was confirmed at the American Academy of Orthopaedic Surgeons/National Institutes of Health Optimizing Clinical Use of Biologics Symposium in 2018. A working group of 6 experts convened an international consensus process involving clinicians and basic scientists using validated Delphi methodology. This iterative process was used to define statements on communication of cell therapies and develop a standardized tool for describing cell therapies.

Results: Thirty-four experts completed 3 rounds survey with use of the Delphi process. After 3 rounds, 27 statements relating to existing nomenclature, solutions to improve communication, ideal characteristics of a framework, mandatory elements of a new framework, and future work to facilitate application reached consensus with >80% agreement and <5% disagreement. Consensus was reached on the contents of a tool for improving standardization and transparency when describing cell therapies. This tool, dubbed "DOSES," is based on the reporting of 5 core items: donor (i.e., autologous, allogeneic, xenogeneic), origin of tissue, separation from other cell types/preparation method, exhibited cell characteristics associated with behavior, and the site of delivery.

Conclusions: This study has established expert consensus on the communication of cell therapies. The DOSES tool has been developed to improve standardization and transparency in describing cell therapies.

Clinical Relevance: The DOSES tool for describing cell therapies can be utilized by researchers, clinicians, regulators, and industry professionals to improve standardization and transparency when describing cell therapies. The use of this tool may allow clinicians and patients to better understand the characteristics of current and future cell preparations.

Over the past decade, there has been an exponential growth in the use of cell therapies to treat musculoskeletal disease[1]. Cell therapy involves the delivery of viable cells into a patient to positively influence therapeutic outcomes[2]. Cells delivered can be autologous, allogeneic, or xenogeneic and can range from terminally differentiated adult

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cells and adult multipotent populations to pluripotent populations isolated from embryos or generated from adult cells as induced pluripotent cells. Therapies that claim to contain adult multipotent populations, including cultured mesenchymal stromal cells (MSCs) and unpurified bone-marrow-derived preparations, are the most widely researched, with over 800 clinical trials listed on ClinicalTrials.gov (Fig. 1). To date, results of these studies have generally been disappointing[3], and the widespread use of these treatments is not currently supported by rigorous evidence. Nonetheless, as of May 2017, 716 clinics in the United States alone were engaged in direct-to-consumer marketing of "stem cell"-based interventions, the vast majority of which are promoted for musculoskeletal injuries[4].

The lack of a standardized and transparent system for describing cell therapies has impeded scientific advancement and afforded an opportunity for clinics to potentially exploit ambiguity in definitions and descriptions to provide treatments that may not be evidence-based[5-8]. Although checklists have been generated that set out to encourage the comprehensive reporting of methodology and biologic characteristics in clinical studies[9], there remains no standardized system for describing cell therapies. At present, a myriad of terms is being used to describe cell populations without a clear description of their characteristics or origins[10].

The term "stem cells" is itself being used inappropriately, generating confusion among clinicians, researchers, and patients[11]. MSCs have been defined by these minimal criteria proposed by the International Society for Cellular Therapy (ISCT): (1) MSCs must be plastic-adherent in standard culture conditions; (2) MSCs must express CD105, CD73, and CD90 and lack expression of CD45, CD34, CD14 or CD11b, CD79alpha or CD19, and human leukocyte antigen-DR surface molecules; and (3) MSCs must differentiate to osteoblasts, adipocytes, and chondroblasts in vitro[12]. The term MSC is frequently being applied to populations without these demonstrated attributes.

Misleading or ambiguous terminology can result in mistaken assumptions regarding cell origins and characteristics, making interpretation of studies difficult[9]. A lack of standards for conveying the characteristics of cell therapies is being increasingly exploited with misinformation of unproven treatments[13]. Therefore, a more transparent and standardized system for accurately describing cell therapies used to treat musculoskeletal conditions is mandatory. The purpose of this study was to establish an international expert consensus on strategies to improve transparency and effectiveness of cell therapy communication using Delphi methods. A secondary purpose was to develop consensus among experts on the contents of a standardized tool for describing cell therapies.

Materials and Methods

The need for expert consensus on strategies to improve communication for cell therapies was confirmed at the American Academy of Orthopaedic Surgeons/National Institutes of Health Optimizing Clinical Use of Biologics Symposium in 2018[14]. A working group of 6 individuals (I.R.M, J.C., M.R.S., A.J.K., D.B.F.S., and R.F.L) facilitated the development of consensus with use of modified Delphi techniques[9]. Details of the consensus are presented in Figure 2. In the absence of exact criteria listed in the literature for the selection of Delphi participants, experts were selected in a nomination process by all 6 members of the working group[15]. Although the majority of Delphi studies have utilized between 15 and 20 respondents[15], a larger group of 30 to 40 experts was sought to increase representation in this broad field. For inclusion, all nominated individuals had to fulfill the following criteria: (1) clinician, clinician scientist, or basic scientist; (2) active leadership or senior involvement in studies relating to cell therapies; and (3) affiliation with an academic institution or research institute. All 36 individuals identified in the first round of nominations met the criteria for eligibility. All members of the working group were satisfied that the group was representative of the wider international community of academics working in cell therapies. All 36 experts identified were invited by e-mail to take part in a Delphi project relating to the communication of cell therapies. There

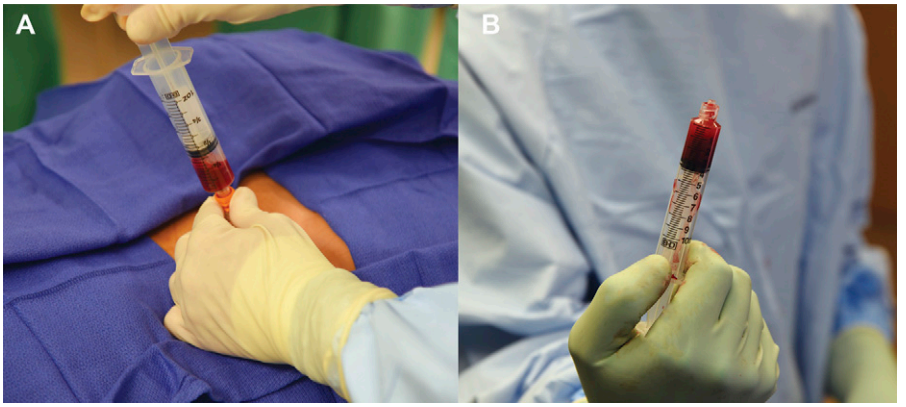

Fig. 1

Figs. 1-A and 1-B Bone marrow is harvested from sites such as the iliac crest. In orthopaedics, bone marrow is often concentrated by centrifugation prior to injection into joints, tissue, or the blood system. The popularity of "stem cell"-containing products, such as bone marrow aspirate concentrate, has been driven by ease of use and direct-to-consumer marketing.

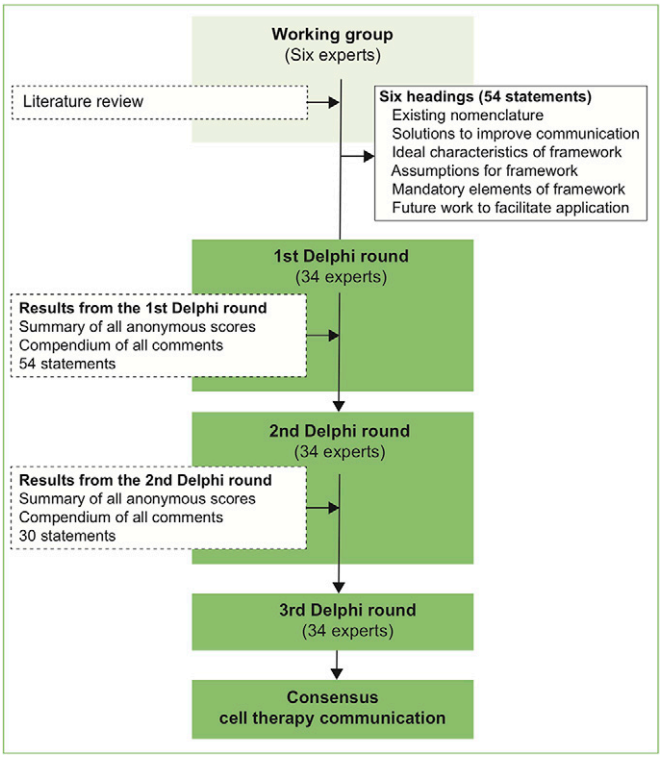

Fig. 2

Flowchart showing the consensus process.

were 2 non-respondents following a single additional reminder of invitation. Of the 34 experts who agreed to take part, 19 (56%) were from North America, 11 (32%) were from Europe, 2 (6%) from South America, and 2 (6%) from Asia; 10 (29%) were basic scientists and 24 (71%) were orthopaedic clinicians or clinician scientists.

In order to generate the items for rating within the first-round survey, the working group reviewed factors relating to deficiencies of current cell therapy nomenclature. Discussions were based on a review of papers identified in recently published systematic reviews that evaluated cell therapies for musculoskeletal pathology, with a focus on items that may guide the development of a tool to improve transparency in the description of cell therapies. Draft statements were then generated. An online survey was created allowing experts to rate agreement on a Likert scale[16]: "strongly agree," "agree," "neither agree nor disagree," "disagree," or "strongly disagree." A free-text comments section was included to enable suggestions of modifications or additional items. These inputs were integrated and amended consensus statements were prepared. In the second round, participants were asked to review the anonymized results from round 1 and score all items within the second survey. As with round 1, a free-text comments section was included to allow for suggestions of modifications or additional items. Questionnaires were reanalyzed and the cycle was repeated. The process was continued until a consensus was reached for all items as defined below, or for a maximum of 3 rounds.

Levels of agreement required for inclusion within subsequent Delphi rounds and within the final consensus survey were defined *a priori*. Following round 1, items with >70% agreement and <20% disagreement were retained for round 2. Items not meeting these criteria were discarded or modified per the suggestions of responders. Responses were analyzed with stricter cutoff criteria in round 2, with items retained only if >70% agreement was reached and <10% of experts disagreed. Items surveyed in the third round were included in the final consensus if >80% of respondents agreed and <5% disagreed.

Results

Delphi Process and Overall Consensus

From group discussions and a review of existing related literature, the working group identified 54 statements for consideration by the expert group in the first round. Items were categorized under 6 headings: existing nomenclature, solutions to improve communication of cell therapies, ideal characteristics of a framework for communicating cell therapies, assumptions made when considering a new framework, mandatory elements of cell therapy for describing cell therapies, and future work to facilitate application. Thirty-four experts completed all 3 rounds of the survey. The results of each round of the survey are summarized in Table I. Consensus was achieved in 27 items relating to strategies for improving standardization and transparency when describing cell therapies (Table I). All 27 items (100%) included within the final survey achieved consensus, with >80% of experts in agreement and <5% in disagreement (Fig. 3, Table II). The levels of agreement for items not meeting criteria for consensus at each round are shown in Appendix Table E-I.

Consensus Findings

Five principal domains were identified within the consensus, with critical elements discussed below.

TABLE I Summary of Results at Completion of Each Survey Round in the Delphi Process

Delphi Round	Responses	Total Items Included in Survey	Existing Items Reaching Consensus	New Items or Modifications Suggested
1	34	54	89%	14
2	34	30	97%	6
3	34	27	100%	0

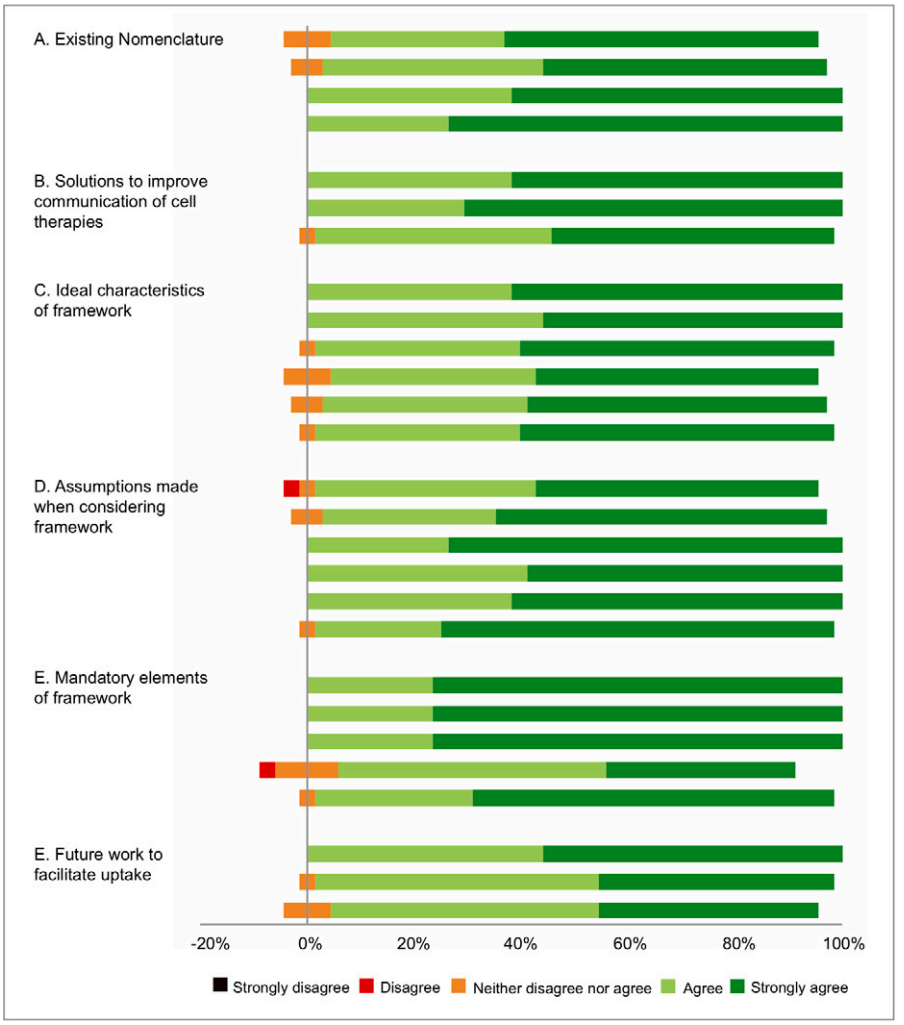

Fig. 3

Stacked leaning bar chart representing breakdown of agreement levels in the third-round Delphi survey.

Existing Nomenclature

There has been an increase in cell therapies utilized to treat musculoskeletal pathology[17,18]. However, the current use of ambiguous terms to describe cell therapies is limiting scientific progress and consumer understanding[14]. The term "stem cells" is frequently used as a marketing tool, leading many patients to believe that the therapy exerts a therapeutic effect by replacing damaged or lost cells[1,2,19,20]. This term is frequently used to describe cell preparations in the absence of demonstrated multipotency and self-renewal, creating substantial confusion for patients, physicians, and the public[21-23]. The majority of experts agreed with the rigorous use of the ISCT standard for defining a cell population as an MSC (61% agreed and 18% disagreed). However, agreement did not reach the threshold of 80% set for the present study. The ISCT standard was, therefore, not included in this consensus statement, but it is by no means rejected as a valuable standard for rigor in nomenclature in the field. There was little disagreement (only 3%) on the point that future frameworks for describing cells should be compatible with existing systems of cell description.

Solutions to Improve Communication of Cell Therapies

The scientific community has a responsibility to address deficiencies relating to inadequate cell therapy terminology and communication. Researchers, clinicians, and commercial providers should describe their product accurately and transparently.

A majority of experts believed that scientific understanding was insufficient to enable the development of a hierarchical classification system, although this did not meet consensus criteria (71% agreed and 12% disagreed). However, there was consensus that a system for describing cells with certain critical features of cell processing or characteristics will improve transparency and understanding and would be worthwhile (97% agreed and 0% disagreed).

It was agreed by a majority of experts that a tool mandating the description of critical aspects of processing or characteristics should be applied to all cell types, accommodating future populations not yet discovered. As a result, providers of cell therapies that are reported "novel" and cannot be classified within the existing framework[4,18]

TABLE II Levels of Agreement and Disagreement for the Items Included in the Round-3 Survey

	% Disagreement	% Agreement
Existing nomenclature		
There has been an increase in cell therapies used to treat musculoskeletal pathology.	0	91
The current use of ambiguous terms to describe cell therapies is limiting scientific progress.	0	94
Ambiguous terminology has a detrimental effect on consumer understanding of treatments.	0	100
The term "stem cells" to describe cell preparations in the absence of demonstrated multipotency and self-renewal creates substantial confusion for patients, physicians, and the public.	0	100
Solutions to improve communication of cell therapies		
The scientific community has a responsibility to address deficiencies relating to inadequate cell therapy terminology.	0	100
Researchers, clinicians, and commercial entities should describe their product in a manner that is accurate and transparent.	0	100
The reporting of certain critical features relating to cell processing or characteristics (known as "core descriptors") will improve transparency and understanding.	0	97
Ideal characteristics of a "core descriptors/attributes" framework		
An ideal framework for describing cell therapies should encourage standardization in reporting.	0	100
An ideal framework for describing cells therapies should encourage transparency of cell characteristics.	0	100
A new framework for describing cells should incorporate available information that may critically influence cell behavior.	0	97
An ideal framework would accommodate forthcoming technologies and understanding that we do not currently have.	0	91
A new "core descriptors" framework should include sufficient items to enable appreciation of cell therapy attributes.	0	94
The number of items included in a new "core descriptors" framework should not be so onerous as to prevent uptake as a communication tool or to act as a barrier to research and development.	0	97
Assumptions made when considering a framework for communicating cell therapies		
Cell therapies represent a complex mixture of cells, growth factors, and cytokines in variable compositions.	3	94
Donor factors may critically influence cell characteristics (e.g., age, sex, genomic and epigenetic factors).	0	94
The distinction between autologous, allogeneic, and xenogeneic sources of cells is important.	0	100
The tissue type of origin (e.g., bone, fat) may influence cell characteristics.	0	100
The cellular composition of preparations (including presence of non-regenerative cells) may influence therapeutic effect.	0	100
Methods of preparation may influence behavior, including (1) "minimal manipulation" processing techniques (i.e., mechanical disruption, centrifugation), (2) laboratory culture, and (3) purification through affinity-based separation (i.e., FACS, MACS).	0	97
Mandatory elements of a framework for communicating cell therapies. A framework requiring the reporting of "core descriptors/attributes" of cell preparations should include the following items:		
A distinction between autologous, allogeneic, and xenogeneic donor source.	0	100
The tissue of origin (e.g., fat, bone marrow).	0	100
Methods of preparation including (1) "minimal manipulation" processing techniques (i.e., mechanical disruption, centrifugation), (2) laboratory culture, and (3) purification through affinity-based separation (i.e., FACS, MACS) should be reported.	0	100
Expression of confirmed cell surface markers should be stated (or indicated if not tested).	3	85
The method of delivery (i.e., intra-articular, intravenous) should be stated.	0	97
Future work to facilitate a comprehensive and prognostic classification system		
Researchers, clinicians and commercial entities should report the items considered "core descriptors" when communicating regarding cell therapies.	0	100
Regulators, societies, and funding bodies should make the reporting of the above "core descriptors" mandatory when any product involving cell therapies is discussed.	0	97
Journals should make the reporting of "core descriptors" mandatory when authors describe a cell therapy.	0	91

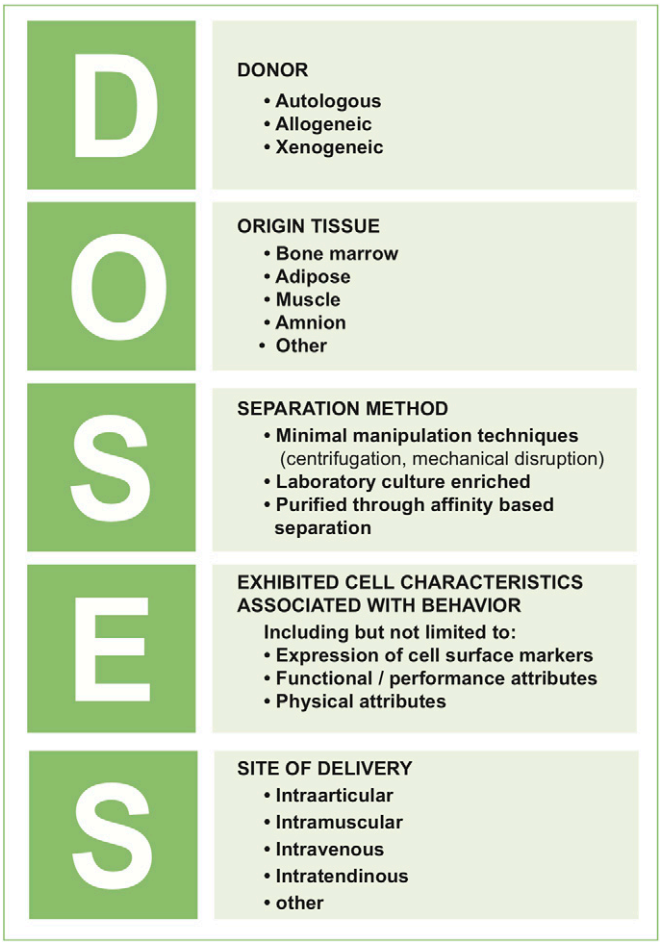

Fig. 4
Summary of the "DOSES" cell-therapy communication tool.

could instead utilize the system proposed above. Furthermore, it was clear that a descriptive tool would not seek to replace existing nomenclature or terminology, but rather encourage transparency and clarity when describing any given population in a system that could be universally applied.

Ideal Characteristics of a Framework

An ideal framework for describing cell therapies should encourage standardization and transparency and include information that may critically influence cell behavior. An ideal framework would accommodate forthcoming technologies and understanding. A new tool should include sufficient items to enable appreciation of cell therapy attributes but not be so onerous as to prevent uptake as a communication tool or to act as a barrier to research.

Assumptions Made When Considering a Framework for Communicating Cell Therapies

Cell therapies often represent a complex mixture of cells, growth factors, and cytokines in variable compositions[10,24-26]. The distinction between autologous, allogeneic, and xenogeneic sources of cells is important. The tissue type of origin and donor factors may critically influence cell characteristics. The cellular composition of preparations, including the presence of non-regenerative cells, may influence the therapeutic effect. Methods of preparation may influence behavior, including (1) "minimal manipulation" processing techniques (e.g., mechanical disruption or centrifugation), (2) laboratory culture, and (3) purification through affinity-based separation (i.e., fluorescence-assisted cell sorting [FACS] and magnetic-activated cell sorting [MACS]).

Mandatory Elements of a Framework for Communicating Cell Therapies (DOSES)

Consensus was reached on the inclusion of the following items within a cell therapy communication tool: (1) a distinction between autologous, allogeneic, and xenogeneic donor source should be made; (2) the tissue of origin (e.g., fat, bone marrow) should be stated; (3) methods of preparation, including "minimal manipulation" processing techniques (e.g., mechanical disruption or centrifugation), laboratory culture, and purification through affinity-based separation (i.e., FACS or MACS) should be reported; (4) expression of confirmed cell surface markers should be stated (or indicated if not tested); and (5) the method of delivery (i.e., intra-articular, intravenous) should be stated.

These 5 items formed the foundation for the cell-communication tool dubbed "DOSES" (Fig. 4). In practice, health providers or researchers would be encouraged to use the DOSES tool as the basis for a description of any cell therapy. This tool could be used when authors first introduce a cell population in a manuscript and when commercial entities introduce a product to providers and consumers. The DOSES tool is not intended to provide an exhaustive description of all cell attributes that may influence behavior, but rather to provide sufficient information to enable rapid indication of core attributes to facilitate efficient communication. As such, the tool should not be considered a replacement for the use of existing checklists for minimum reporting standards of methodology details, such as the CONSORT (Consolidated Standards of Reporting Trials)[27] or MIBO (Minimum Information for Studies Evaluating Biologics in Orthopaedics)[9] checklists.

Examples of use of the DOSES tool are: (1) bone marrow MSCs (DOSES: autologous, bone-marrow-derived, FACS-purified and culture-expanded cells, with 90% viability and expressing CD90 and CD146, intra-articular delivery); (2) bone marrow aspirate concentrate (DOSES: autologous, bone-marrow-derived, minimally manipulated through centrifugation, with 80% viability and unknown cell surface marker expression, intra-articular delivery).

There has been increasing skepticism regarding the cell surface marker phenotype of MSCs within the ISCT definition[28]. The DOSES tool encourages users to report all markers characterized without an artificial focus on existing panels that are increasingly controversial.

Future Work to Facilitate a Comprehensive and Prognostic Classification System

Consensus was reached that researchers, clinicians, and commercial entities should use this tool when communicating cell therapies. Furthermore, 97% of experts agreed that regulators, societies, and funding bodies should make the reporting of the above tool mandatory when any product involving cell therapies is discussed, and journals should mandate the disclosure of these critical factors when authors describe a cell therapy. Adherence to the use of the DOSES tool may best be achieved by expanding the discussion to include a larger community to enable consensus among relevant professional societies and standards organizations. We believe that the DOSES tool may be helpful for applications beyond the musculoskeletal system; however, further studies including representative expert panels from these fields would be of value.

Discussion

The most important finding of the present study was the consensus among experts that the current use of ambiguous terms to describe cell therapies is limiting scientific progress and that there is a need for tools to facilitate transparency in communication. Clinical research and practice are being undermined by ambiguous terminology that acts as a barrier to understanding the basic attributes of cell therapies. The present study has established consensus on the requirement for a descriptive tool to improve cell therapy communication. Through 3 Delphi rounds, 34 experts agreed on the inclusion of 5 distinct items within a descriptive communication tool. This tool will allow researchers, clinicians, funding bodies, and commercial entities to rapidly communicate critical aspects of a cell preparation in a standardized fashion. Although a stated advantage of this tool is the applicability to future cell types and technologies, the DOSES tool should undergo future reappraisal and, if necessary, modifications.

The Delphi methods utilized in this study offer several advantages over group-based methods[29]. Anonymity of responses reduces the effects of dominant individuals[29]. Online methods are as reliable as face-to-face panels[30], improving rather than jeopardizing the quality of results. The high response rate across all 3 survey rounds in both Delphi studies demonstrates engagement with the process by all experts. The strict criteria for inclusion in the final statement (>80% experts agreeing and <5% experts disagreeing) were set more tightly than in most published Delphi studies[31] to ensure that only items reaching high levels of agreement were included.

We recognize that this study had some limitations. Although Delphi panel methodology facilitates a more scientific approach to consensus than popular nominal group techniques[32], it does not avoid the potential risk of bias in the selection of participants. It is possible that individual biases relating to the involvement with industry may have influenced certain responses. In selecting experts, the working group sought to minimize bias by including experts from different backgrounds, working in a range of clinical settings, with representation from all continents[15,33]. Although as few as 10 experts are considered adequate for content validation[34], a larger group was chosen to increase representation in this broad field. The potential influence of any single individual was reduced by including more experts than most published Delphi studies and by setting the threshold levels of agreement for consensus high. Although experts were drawn from throughout Europe and Asia, the majority were based in North America. Efforts to establish if these standards are practical and generalizable to other populations may be merited.

In summary, the development of an international consensus on strategies to improve transparency and understanding when communicating about cell therapies has been presented. The DOSES tool can be utilized by researchers, clinicians, regulators, and industry professionals to improve standardization and transparency when describing cell therapies. In detailing key features of cells, the use of this tool may allow clinicians and patients to better understand the characteristics of current and future cell preparations.

Appendix

eA Supporting material provided by the author is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/F192). ■

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